REMARKS

On June 26, 2003, Applicants filed a response under the voluntary revised amendment practice guidelines to the Office Action dated February 26, 2003. The Examiner responded with a Notice of Non-Compliant Amendment dated July 2, 2003, noting that Applicants' Amendment did not include a status identifier for each pending claim pursuant to the revised amendment guidelines. Applicants were given one month to re-submit the Amendment in proper format. Applicants thank the Examiner for his detailed review of the previously submitted Amendment and apologize for any convenience. Applicants have corrected their inadvertent error with this submission, including a status identifier for each pending claim.

Status of the Claims.

Claims 2-13, 17-23, and 51-64 are pending with entry of this amendment. Claims 2, 3, and 18 are amended herein. The amendments to the pending claims introduce no new matter and are fully supported by the specification as filed. Claims 1, 14-16, and 65-67 were previously canceled without prejudice to subsequent renewal. Claims 24-50, which were previously withdrawn from further consideration as being drawn to a non-elected invention, are canceled herein without prejudice to subsequent renewal in a continuation or divisional application.

Rejections Under 35 USC § 112.

Claims 18-23, 51-58, and 64 remain rejected under 35 USC § 112, second paragraph, as allegedly being incomplete for omitting essential steps, such omission amounting to a gap between the steps. The Examiner finds the omitted steps are: "how to determine whether the recombinant cell-specific binding moiety polypeptide has an enhanced ability to bind to the target cell, which is the control that is compared to determine enhanced ability to bind the target cell." Office Action, p. 2.

As the Examiner notes, Applicants previously amended claim 18 to provide specifically in step (5): "determining which of the one or more recombinant cell-specific binding moiety polypeptides exhibits an enhanced ability to bind to the target cell ***compared to the***

ability of a binding moiety polypeptide encoded of (1) to bind to the target cell (emphasis added). The Examiner finds that this previous amendment "was not persuasive because step (1) of claim 18 is to recombine first and second forms of at least one nucleic acid that encodes a binding moiety polypeptide of an enterotoxin to produce a library of nucleic acids. Step (1) of claim 18 is directed to sing nucleic acids to establish a library but not a binding moiety polypeptide. Further, there are more than one and could have [been] hundreds of different nucleic acids encoding binding moiety polypeptides of enterotoxin. It is unclear which binding moiety polypeptide is being compared to determine enhanced ability to bind target cells." Office Action, pp. 2-3. Claim 51 was similarly amended, and the Examiner finds that the amendments to claim 51 failed to clarify the indefiniteness for the same reasons.

Applicants respectfully traverse this rejection of claims 18 and 51 as follows.

In traversing the indefiniteness rejection, Applicants first note that step (5) of claim 18, as previously amended, included a typographical error. The word "encoded" was inadvertently included in step (5). Step (5) of claim 18 has been amended to delete this word.

Applicants respectfully submit that the Examiner has misunderstood claims 18 and 51. Step (1) of claim 18 specifies recombining at least first and second forms of at least one nucleic acid, ***wherein each of the first and second forms of the nucleic acid comprises a polynucleotide which encodes a binding moiety polypeptide of an enterotoxin***, wherein the first and second forms differ from each other in two or more nucleotides, to produce a library of recombinant nucleic acids (emphasis added). Applicants respectfully point out that claim 18 expressly provides that each of the at least first and second forms of the nucleic acid included in the recombination encodes a binding moiety polypeptide of an enterotoxin. Step (1) further specifies that the at least first and second forms of the nucleic acid are recombined to produce a library of ***recombinant nucleic acids***. Step (3) indicates that one or members of the library of recombinant nucleic acids are expressed to form one or more ***recombinant cell-specific binding moiety polypeptides***. Step (4) specifies contacting one or more of the recombinant cell-specific binding moiety polypeptides with a cell surface receptor of a target cell. Step (5) specifies determining which of the recombinant cell-specific binding moiety polypeptides exhibits an enhanced ability to bind to the target cell compared to the ability of a binding moiety polypeptide

of step (1) to bind to the target cell. Thus, the ability of a resultant recombinant cell-specific binding moiety polypeptide to bind the target cell is compared with the ability of a particular binding moiety polypeptide that is encoded by one of the particular starting nucleic acids to bind a target cell. As drafted, claim 18 is plainly clear. The specific starting nucleic acids and the polypeptides they encode are clear. The comparison is also clear. One simply determines which of the recombinant cell-specific binding moiety polypeptides has an enhanced ability to bind the target cell compared to the ability of the binding moiety polypeptide encoded by a specific (starting) nucleic acid used in the recombining step of (1) to bind the target cell.

The same analysis applies to independent claim 51. Claim 51 plainly specifies determining which of the resultant recombinant cell-specific binding moiety polypeptides has an enhanced ability to bind the target cell compared to the ability of the binding moiety polypeptide encoded by a particular nucleic acid included in the recombination, as set forth in step (1), to bind the target cell.

Independent claims 18 and 51, and claims dependent thereof, are precisely drafted and are not indefinite. Each claim sets out and circumscribes a particular area that Applicants regard as the invention with a reasonable degree of precision and particularity and thus fully satisfies the requirements of § 112, second paragraph. Neither claim 18 nor claim 51 (nor any claim dependent thereon) is incomplete. Neither claim 18 nor claim 51 (nor any claim dependent thereon) omits any essential step. Nor does either claim 18 or 51 (nor any claim dependent thereon) fail to interrelate essential elements of the invention as defined by Applicants in the specification. *See* MPEP § 2172.01. On the contrary, as shown above, the relationship between the elements of each of claims 18 and 51 is clearly described.

The Examiner appears to suggest that one of skill in the pertinent art would not know how to determine whether a recombinant cell-specific binding moiety polypeptide has an enhanced ability to bind to the target cell. This finding is also misplaced. Under 35 USC § 112, second paragraph, definiteness of claim language is analyzed in light of the content of the specification, the teachings of the prior art, and the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the application was filed. One skilled in the art at the time the application was filed would have no difficulty understanding

or practicing the methods defined by either claim 18 or claim 15 in view of the description provided in the specification. Applicants provided specific guidance throughout the specification on various ways in which determine whether a recombinant cell-specific binding moiety polypeptide has an enhanced ability to bind to the target cell compared to the ability of a binding moiety polypeptide encoded by one of the nucleic acids in the recombining step to bind the same target cell (see the specification, including at, but not limited to, e.g., p. 23, line 22 to p. 26, line 27). Furthermore, many techniques for assessing protein binding (such as binding between a ligand and a receptor protein on a target cell) were known and/or routine in the art at the time of filing. Moreover, the *particular* technique be used to evaluate binding to a target cell is not an essential element or step of claim 18 or 51, or any claim dependent thereon.

For at least these reasons, Applicants believe the rejection of claims 18-23, 51-58, and 64 is improper and respectfully request that it be withdrawn.

Claims 2-13 and 59-63 were rejected under 35 USC § 112, second paragraph, as allegedly being incomplete for omitting essential steps, such omission amounting to a gap between the steps. Office Action, p. 3. Specifically, the Examiner finds the omitted steps are: "how to determine whether the recombinant cell-specific binding moiety polypeptide has an ability to increase uptake or specificity of a genetic vaccine for a target cell, which is the control that is compared to determine enhanced ability to bind the target cell." *Id.* This rejection is overcome by the amendments to independent claim 2 and claim 3 dependent thereon. As amended, claim 2 now provides more particularly in (6) as follows:

> (6) determining if one or more target cells contain a vector from the vector-binding moiety complex, *comparing the percentage of target cells containing the vector from the vector-binding moiety complex with the percentage of target cells containing a control binding moiety after contacting the control binding moiety with one or more target cells, wherein the control binding moiety comprises a nucleic acid binding domain and cell-specific ligand of (1),* and recovering the recombinant cell-specific binding moiety nucleic acid from any such target cells.

Claim 3 has been similarly amended and now recites more particularly in (11) as follows:

> (11) contacting the vector-binding moiety complex of (10) with a target cell of interest, determining if one or more target cells contain a vector from the vector-binding moiety complex of (10) *and comparing the percentage of target cells containing the vector from the vector-binding moiety complex with the percentage*

of target cells containing the control binding moiety after contacting the control binding moiety with one or more target cells;. . .

With these amendments to claims 2 and 3, Applicants believe that the rejection of claims 2-13 and 59-63 is overcome. Withdrawal of the rejection is respectfully requested.

Claims 2-13 and 59-63 were rejected under 35 USC § 112, second paragraph, as allegedly being indefinite for failing to distinctly point out and distinctly claim the subject matter which Applicants regard as their invention. Office Action, p. 3. The Examiner finds that step (1) of claim 2 is vague and renders the claims indefinite. Specifically, the Examiner is of the view that it is unclear how the polynucleotide encoding a nucleic acid binding domain is associated with the polynucleotide encoding a cell-specific ligand in the library of recombinant binding moiety-encoding nucleic acids and whether the polynucleotide encoding a nucleic acid binding domain is covalently bound or fused to the polynucleotide encoding a cell-specific ligand or whether they are separate from each other. *Id.* This rejection has been overcome by amending claim 2 to recite more particularly that a recombinant binding moiety-encoding nucleic acid comprises a polynucleotide encoding a recombinant nucleic acid binding domain fused or covalently linked to a polynucleotide encoding a recombinant cell-specific ligand.

Claims 2-13, 17-23, and 51-64 were rejected under 35 USC § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which the invention pertains, or with which it is most clearly connected, to make and/or use the invention. Office Action, p. 4. Specifically, the Examiner takes the position that:

> The specification fails to provide adequate guidance and evidence for how the polynucleotide encoding a nucleic acid binding domain is associated with the polynucleotide encoding a cell-specific ligand in the library of recombinant binding moiety-encoding nucleic acids. Does [sic] those two polynucleotides are fused together or they are on separate vectors? The specification fails to provide adequate guidance an evidence for how the expression products of these two polynucleotides would form a recombinant binding-moiety and how to use said binding moiety to bind a vector and screen for recombinant cell-specific binding moiety and nucleic acid encoding said moiety having enhanced ability for uptake and binding to target cells *in vitro* and *in vivo*. The specification also fails to provide adequate guidance and evidence how the vector of the vector-binding

> moiety complex would get into the target cell for screening the destined recombinant cell-specific binding moiety when the expressed nucleic acid binding domain and cell-specific ligand are expressed separately and are not associated with each other.

Office Action, pp. 5-6.

The Examiner also finds the claims read on gene transfer *in vivo* and recovery of expressed gene product *in vivo*. In particular, the Examiner finds:

> The specification fails to provide adequate guidance and evidence how to obtain or screen a recombinant binding moiety, comprising a nucleic acid binding domain and a cell specific ligand, or a recombinant binding moiety polypeptide of enterotoxin having enhanced ability for uptake and binding to target cells *in vivo*. The biological environment *in vivo* is very different from the biological environment in vitro. The factors in *in vitro* environment were well controlled. . . there are various unknown bioactive factors that can not [sic] be controlled *in vivo* and these bioactive factors interact with each other and with various regulatory elements. It was known ion the art that a gene which is expressed *in vitro* is not necessarily to be expressed *in vivo* in various cell types because the microenvironment *in vitro* is different from the microenvironment in vivo. Further, Eck et al., 1996 (Goodman and Gilman's The Pharmacological Basis of Therapeutics, Mc-Graw Hill, NY, pp. 77-101) states that the fate of the DNA vector itself, the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene transfer *in vivo* (e.g. bridging pages 81-82). In addition, administration routes and type of target cells for gene expression also affect the expression of the nucleic acid binding domain and cell-specific ligand *in vivo*.

Office Action, pp. 6-7.

Based on these findings, the Examiner concludes that one skilled in the art at the time of the invention would have to have engaged in under experimentation to practice the full scope of the invention, particularly "given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the absence of working examples and scarcity of guidance in the specification, and the unpredictable nature of the art." *Id.* at p. 7.

Applicants respectfully traverse this rejection as follows. Section 112, first paragraph, imposes two basic enablement requirements. An applicant for a patent must adequately disclose to those of ordinary skill in the pertinent art, in light of what is known in the art, how to make the claimed invention and how to use the claimed invention throughout its scope without undue experimentation. Whether a disclosure is sufficient to enable one of ordinary skill in the art to practice the claimed invention throughout its scope without having to engage in undue experimentation may be assessed by weighing a variety of factors. In *In re Wands*, 858 F.2d 731, 737, 8 UPSQ2d 1400, 1404 (Bd. Pat. App. & Int. 1986), the Board of Patent Appeals and Interferences outlined the following factors for consideration: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance; (3) the presence of absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims.

Based on a review of these factors, Applicants submit that the disclosure of the present application clearly provides reasonable guidance to one skilled in the pertinent art to practice the claimed invention throughout its scope without undue experimentation. Independent claim 2, for example, is directed to a specific method for obtaining a recombinant cell-specific binding moiety for an ability to increase uptake or specificity of a genetic vaccine for a target cell. Independent claims 18 and 51, for example, define particular methods for obtaining a recombinant cell-specific binding moiety for an ability to increase uptake, efficacy, or specificity of a vaccine or antigen for a target cell. These claimed methods are straightforward; each step of each method is explicitly defined. In addition, the guidance and direction given by the specification is entirely sufficient and adequate to practice these methods. Furthermore, the level of skill of one in the pertinent art at the time of filing the application was at least relatively high, and four working examples are provided in the specification for practicing the claimed invention.

With regard to claim 2, the Examiner appears to be of the opinion that the specification fails to provide adequate guidance and evidence for how the polynucleotide encoding a nucleic acid binding domain is associated with the polynucleotide encoding a cell-specific ligand in the library of recombinant binding moiety-encoding nucleic acids. Office

Action, m pp. 5-6. Based on the disclosure provided in the specification, one of ordinary skill in the art would clearly understand that the recombinant binding moiety-encoding nucleic acid encodes a binding molecule that can bind to a nucleic acid and to a cell-specific receptor. See e.g., p. 2, line 30 to p. 4, line 11, p. 35, line 21 to p. 43, line 16; and Example 3. One of skill in the pertinent art would understand that the two domains can be fused or linked together. For example, the cell-specific binding ligand can be fused or linked to the nucleic acid binding domain such that a protein comprising both domains is produced. Description of such proteins is provided throughout the specification, including at, but not limited to, e.g., p. 42, lines 3-4. p. 39, lines 29-31, p. 38, lines 6-7; and Example 3. Additionally, there is no question that methods for making fusion proteins or proteins comprising two linked domains using standard linkers were well known and commonly practiced in the art at the time of filing. Moreover, claim 2, has been amended to particularly specify that these domains are fused or covalently linked together. In summary, the scope of claim 2 is clear, and the teachings of the specification would reasonably apprise a person of skill in the pertinent art in light of what was well known in the art at the time how to make and use this claimed method throughout its scope.

The Examiner also contends that the specification fails to provide adequate guidance to one skilled in the art as to how to use the recombinant cell-specific binding moiety to bind a vector, how to screen for those recombinant cell-specific binding moiety having enhanced ability to be taken up or bind to target cells *in vitro* or *in vivo*, and how the vector-binding moiety complex would get into the target cells. These contentions also lack merit. The claims and specification plainly describe that binding of the recombinant cell-specific binding moiety to the vector (to make the vector-binding moiety complex) can be carried out, e.g., by contacting the recombinant cell-specific binding moiety with the vector. Such contact can be carried out *in vitro* or *in vivo*. As explained in the specification and as would be known to one of ordinary skill in the art, *in vivo* contact can be accomplished, e.g., by injecting the complex into animal tissue containing the target cells of interest. The tissue or cells from the tissue can then be collected from the animal and analyzed from the presence of the vector. See the specification, including at, but not limited to, e.g., p. 4, line 26 to p. 5, line 22; p. 8, line 28 to p. 9, line 8; p. 26, line 29 to p. 27, line 18; p. 28, line 11-14; p. 30, lines 1-9. A variety of *in vitro* and *in vivo* screening

formats are also expressly described in the specification. For example, in either *in vivo* or *in vitro* format, those cells that take up the vector can be detected by including a selectable or screenable marker or an antigen or other molecule of interest in the vector or by using standard amplification and/or PCR techniques to screen for the presence of the vector. See the specification, including at, but not limited to, e.g., p. 26, lines 6-27; p. 26, line 28 to pg. 27, line 6; p. 27, line 27 to p. 29, line 25; p. 29, line 25 to p. 31, line 6; p. 32, line 1 to p. 43, line 26; Example 4. Plainly, one of skill in the art would understand how to carry out and use the method defined by claim 2 to obtain a recombinant binding moiety (which comprises both a recombinant nucleic acid binding domain and a recombinant cell-specific ligand binding domain) that is better able to facilitate uptake of a genetic vaccine for a target cell than is binding moiety comprising the original domains that have not been recombined.

The Examiner also appears to assert that all of the rejected claims -- claims 2-13, 17-23, and 51-64 -- read on gene transfer *in vivo* and that difficulties associated with gene transfer make the claimed methods unpredictable. This assertion is also misplaced. Gene-based therapy methods pertain to the therapeutic treatment of human disease typically resulting from a defective gene or lack of a needed gene by transfer of the missing or non-defective gene *in vivo* to the individual suffering from the disease. The fact that gene therapy methods have not been entirely successful in therapeutically treating such diseases does not imply that Applicants' particular claimed invention is unpredictable. The claimed methods are simply directed to specific methods of obtaining recombinant cell-specific binding moieties that have an ability to increase uptake or specificity of a vaccine vector or vaccine for a target cell. These methods define particular recombination and screening procedures to obtain improved recombinant cell-specific binding moieties having such abilities. The difficulties recited by the Examiner with regard to *in vivo* gene therapy methods do not properly bear on the ability of one skilled in the art to carry out any of the claimed methods. For example, even if the biological factors of an *in vivo* environment were more difficult to control than the biological factors of an *in vitro* environment, one of skill would be able to carry out the claimed methods without undue experimentation based upon the guidance provided in the specification and the prior art.

Similarly, the factors the Examiner cites as important for successful practice of *in vivo* gene therapy (e.g., "the fate of the DNA vector itself, the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate") do not pertain to successful practice of the claimed methods, since the claimed methods relate to making improved recombinant binding moiety polypeptides that can better facilitate the uptake or specificity of a DNA vaccine vector by a particular target cell. In the claimed methods, a library of recombinant cell-specific binding moiety nucleic acids is generated by the nucleic acid recombination. Those recombinant cell-specific binding moieties expressed from such recombinant nucleic acids that do not bind the target cell, that are not properly expressed *in vivo*, that are degraded, or that are not taken up by the target cell are merely excluded from further analysis. Those recombinant binding polypeptides that have an enhanced ability to bind a target cell can be readily determined by a variety of well known techniques such as, e.g., comparing the binding affinities of the recombinant binding moiety and non-recombined binding moiety for the target cell. Likewise, those recombinant binding polypeptides that have an enhanced ability to enter a target cell so as to better facilitate uptake of a genetic vaccine vector compared to a non-recombinant binding moiety can similarly determined by a variety of techniques, such as, e.g., comparing the percentage of target cells that contain the vector after contact of such cells with the recombinant binding moiety/vector complex versus contact of such cells with a control binding moiety/vector complex. The percentage of vectors that enter the cells is readily determined by, e.g., counting cells expressing a marker expressed by the vectors in the course of transfection. See the specification, including at, but not limited to, e.g., p. 34, line 13 to p. 35, line 5.

In either *in vivo* or *in vitro* format, the claimed methods of the invention do not have to meet the requirements necessary for successful gene therapy, such as, e.g., proof of effective therapeutic treatment of a disease by a transferred gene, long-term durable expression of the transferred gene, validation of gene transfer to a distant bodily organ (such as an organ

with cancer) in an individual without the ability to obtain tissue from the individual's organ to confirm gene transfer and expression in the target cells of interest, *etc.* The unpredictable aspects that may apply to *in vivo* gene therapy are not relevant to the present claimed methods.

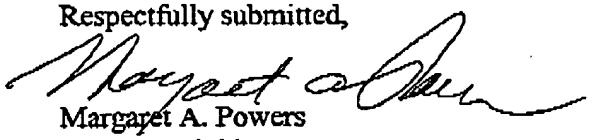
In summary, claims 2-13, 17-23, and 51-64 are narrowly circumscribed and unambiguously defined. Furthermore, the specification provides wholly sufficient guidance to enable one skilled in the pertinent art to carry out and use the claimed invention, as defined by these claims, throughout its scope. Working examples are provided in the specification, and the relative level of skill of one in the art relevant to the invention is comparatively high. Moreover, the relevant art that applies to the claimed invention is not of an unpredictable nature. In addition, an undue amount of experimentation would not be required to carry out the claims. Even if some experimentation were needed to carry out the claimed methods, such experimentation would be permissible. *In re Wands*, 858 F.2d at 737.

For at least these reasons, Applicants respectfully submit that the rejection of claims 2-13, 17-23, and 51-64 is improper and request that it be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe that all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this Application, please telephone the undersigned at (650) 298-5809.

Respectfully submitted,



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